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An investigation of the predictive markers that can be used in the differentiation of benign and malignant lymphadenopathy

Comparison of benign and malignant lymphadenopathy

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Abstract

Aim: Lymphadenopathy (LAP) can develop for many infectious, rheumatological, immunological, and hematological reasons. The most important point for patients presenting with LAP is the decision-making for further tests to identify who should undergo a biopsy and who should be followed up. This study aimed to investigate predictive markers that can be used to differentiate benign and malignant LAP.

Material and Methods: The study included 274 patients who presented at the Hematology Polyclinic with a diagnosis of LAP. Markers were investigated to determine which affected prognosis in patients with a histopathological benign or malignant LAP diagnosis.

Results: Age, male gender, ferritin, lactate dehydrogenase (LDH), C-reactive protein (CRP), LAP located in the neck, thorax, and abdomen, the size of LAP situated in the neck, and the presence of splenomegaly, were determined at statistically significantly higher rates, and hemoglobin, hematocrit, platelet count, plateletcrit (PCT), and folate were statistically significantly lower in the group with malignant LAP. The results of multivariate analysis showed that age, gender, PCT, sedimentation value, thorax LAP, and inguinal LAP were independently significant in the differentiation of patients with benign and malignant LAP.

Discussion: LAP is a frequently encountered pathology but biopsy and further tests may not be appropriate for every patient in terms of cost and workload. Therefore, predictive parameters will be of guidance to the clinician at the stage of decision-making. These parameters will avoid tiring the patient and the doctor with respect to unnecessary further tests, and the chance of early diagnosis will not be missed if it is a malignant process.

Keywords

Anemia, C-Reactive Protein, Ferritin, Lymphadenopathy, Lactate Dehydrogenase

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Introduction

The lymphatic system is a complex system that functions in the filtering of toxins and other substances in the body and is involved in circulation. LAP is defined as abnormal swelling formed in the lymph nodes, which can develop for many infectious, rheumatological, immunological, and hematological reasons [1]. The most important point for patients presenting with LAP is the decision-making for further tests to identify who should undergo a biopsy and who should be followed up. Many factors such as LAP localization, size compared to the site of localization, texture, whether localized or spread, mobile or fixed, and additional complaints (fever, night sweats, weight loss), can help the clinician in decision-making [2]. Although many laboratory and examination findings will guide the clinician in this decision, there is still a need for additional parameters. Therefore, this study aimed to investigate the presence of markers affecting prognosis in patients with a histopathological diagnosis of benign and malignant LAP from biopsy.

Material and Methods

The study included 274 patients who presented at the Hematology Polyclinic of Dışkapı Yıldırım Beyazıt Training and Research Hospital with a diagnosis of LAP between May 2019 and August 2022. A record was made for each patient of demographic characteristics, blood group, hemogram, anemia parameters, CRP, sedimentation rate, LAP localization and size, hepatosplenomegaly, the type of biopsy taken, and pathological result.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 28.0 software. Descriptive statistics were stated as mean ± standard deviation (SD), median, minimum and maximum values, or number (n) and percentage (%). The distribution of the variables was examined with the Kolmogorov-Smirnov test. In the analysis of independent quantitative data, the Independent Samples t-test and the Mann-Whitney U-test were used. The Chi-square test was applied in the analysis of independent qualitative data. The effect level of parameters was investigated with univariate analysis and multivariate logistic regression analysis. A value of $p<0.05$ was accepted as the level of statistical significance.

Ethical Approval

All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital (Date: 2022-03-07, No: 132/11).

Results

A total of 274 patients were analyzed, comprising 127 (46.4%) males and 147 (53.6%) females with a mean age of 50.2±16.5 years. The demographic characteristics and descriptive parameters of the patients are shown in Table 1.

Neck LAP was seen in 75.2% of the patients; the average size was 23.9± 10.6 and the most common locations were left cervical and right cervical (31.1%, and 27.7% respectively). Supraclaviculer LAP was seen in 16.8 % of the patients; the average size was 22.9±10.1 and the most common locations were left supraclaviculer (67.4%). Thorax LAP was seen in 26.3 % of the patients; the average size was 21.2 ± 13.6 and the most common locations were hilar (47.2%). Axillary LAP was seen in 62.3 % of the patients; the average size was 26.7 ± 12.8 and the most common locations were left axillary (54%). Abdomen LAP was seen in 20.4 % of the patients; the average size was 34.8 ± 25.3 and the most common locations were paraortic (53.6%). Inguinal LAP was seen in 57.7 % of the patients; the average size was 25.3 ± 15.0 and the most common locations were right ınguinal (57.6 %). Splenomegaly was detected in 15% of the patients and hepatomegaly in 25.5%.

The patients who presented with LAP were analyzed in two groups 130 (47.4%) patients with a histopathological diagnosis of benign LAP and 144 (52.6%) with malignant LAP. In the group with malignant LAP, age, male gender, ferritin, LDH, CRP, LAP located in the neck, thorax, and abdomen, the size of LAP situated in the neck, and the presence of splenomegaly, were

Table 1. The Demographic and Basic Descriptive Statistics of the Patients

		Mean±SD/n-%		
Age (years)		50.2	±	16.5
Gender	Female	147		53.6%
	Male	127		46.4%
HB		12.7	±	2.4
HCT		38.8	±	6.6
PLT (x10³)		262.4	±	108.9
WBC (x10³)		10.2	±	14.0
Lymphocytes (x10³)		3.2	±	10.7
MPV		9.4	±	1.3
Monocytes		677.8	±	453.3
Neutrophil (x10³)		5.9	±	6.2
PCT		0.2	±	0.1
PDW		13.2	±	3.0
B12		354.0	±	296.5
Folate		7.1	±	4.1
Ferritin		560.3	±	3786.9
LDH		276.0	±	319.6
Sedimentation rate		27.0	±	25.5
CRP		30.9	±	51.2
Group	Benign	130		47.4%
	Malignant	144		52.6%
		n		%
Biopsy LAP site-1				
Right Axilla		28		10.3%
Right Cervical		38		14.0%
Left Axilla		37		13.6%
Left Inguinal		25		9.2%
Left Cervical		40		14.7%
Biopsy Method				
Excision		113		41.2%
FNAB		108		39.4%
Tru-Cut		53		19.3%

HB:hemoglobin, HTC: hematocrit, PLT:Platelet, WBC: White Blood Cell, MPV: Mean Platelet Volume PCT: Plateletcrit, PDW: Platelet Distribution Width, LDH: Lactate Dehydrogenase, CRP: C- Reactive Protein, FNAB: Fine Needle Aspiration Biopsy

Table 2. Comparisons of the Parameters of the Benign and Malignant LAP Groups

		Benign			Malignant			p	
		Mean±SD/n-%			Mean±SD/n-%				
Age (years)		45.0	±	14.4	55.0	±	16.8	0.000	m
Gender	Female	87		66.9%	60		41.7%	0.000	X^2
	Male	43		33.1%	84		58.3%		
HB		13.1	±	2.2	12.4	±	2.6	0.017	t
HCT		40.0	±	5.8	37.7	±	7.1	0.003	t
PLT ($x10^3$)		282.6	±	95.3	244.1	±	117.2	0.003	m
WBC ($x10^3$)		9.5	±	10.7	10.8	±	16.5	0.074	m
Lymphocytes ($x10^3$)		3.2	±	9.2	3.3	±	11.9	0.000	m
MPV		9.6	±	1.3	9.3	±	1.4	0.151	m
Monocytes		658.5	±	467.6	695.2	±	441.0	0.457	m
Neutrophils($x10^3$)		5.3	±	2.8	6.3	±	8.1	0.838	m
PCT		0.3	±	0.1	0.2	±	0.1	0.000	m
PDW		13.2	±	2.8	13.2	±	3.2	0.982	m
B12		325.9	±	211.6	379.5	±	355.1	0.336	m
Folate		7.4	±	3.4	6.8	±	4.7	0.013	m
Ferritin		147.4	±	493.0	933.1	±	5182.9	0.000	m
LDH		221.3	±	116.7	325.3	±	421.3	0.004	m
Sedimentation		21.3	±	23.3	32.2	±	26.4	0.000	m
CRP		17.7	±	36.7	42.7	±	59.1	0.000	m

t Independent Samples t-test / m Mann-Whitney U-test / X^2 Chi-square test
HB:hemoglobin, HTC: hematocrit, PLT:Platelet, WBC: White Blood Cell, MPV: Mean Platelet Volume PCT: Plateletcrit, PDW: Platelet Distribution Width, LDH: Lactate Dehydrogenase, CRP: C-Reactive Protein

Table 3. Logistic Regression Analysis of the Parameters

	Univariate Model					Multivariate Model				
	OR	95% CI			p	OR	95% CI			p
Age	1.041	1.024	-	1.058	0.000	1.024	1.004	-	1.045	0.020
Gender	2.833	1.730	-	4.638	0.000	2.423	1.257	-	4.672	0.008
HB	0.886	0.800	-	0.981	0.019					
HCT	0.946	0.911	-	0.982	0.004					
PLT ($x10^3$)	0.997	0.994	-	0.999	0.004					
Lymphocytes ($x10^3$)	1.001	0.979	-	1.024	0.937					
PCT	0.001	0.000	-	0.025	0.000	0.003	0.000	-	0.182	0.006
Folate	0.965	0.908	-	1.024	0.241					
Ferritin	1.001	1.000	-	1.002	0.002					
LDH	1.003	1.001	-	1.006	0.003					
Sedimentation	1.019	1.008	-	1.030	0.001	1.017	1.002	-	1.031	0.027
CRP	1.012	1.006	-	1.019	0.000					
Neck LAP	0.364	0.202	-	0.655	0.001					
Neck LAP largest diameter	1.046	1.016	-	1.076	0.002					
Thorax LAP	3.109	1.731	-	5.582	0.000	2.155	1.008	-	4.610	0.048
Axillary LAP	0.370	0.221	-	0.617	0.000					
Abdomen LAP	3.832	1.951	-	7.526	0.000					
Inguinal LAP	0.327	0.198	-	0.541	0.000	0.363	0.190	-	0.694	0.002
Splenomegaly	2.480	1.207	-	5.095	0.013					

HB: hemoglobin, HTC: hematocrit, PLT:Platelet, WBC: White Blood Cell, MPV: Mean Platelet Volume PCT: Plateletcrit, LDH: Lactate Dehydrogenase, CRP: C- Reactive Protein

determined at statistically significantly higher rates (p<0.05), and hemoglobin, hematocrit, platelet count, PCT, and folate were statistically significantly lower (p<0.05) (Table 2).

The comparisons of the groups in respect of LAP localization and size. The rates of LAP localization in the thorax (36.1%,15.4%) and abdomen (29.9%, 10.0%) the size of LAP with neck localization (26.4 ±12.1, 21.8±8.6), and the presence of splenomegaly (20.1%, 9.2%) were determined to be statistically significantly higher in the malignant group. LAP with a neck (84.6%, 66.7%) axillary (74.6%, 52.1%), and inguinal (71.5%, 45.1%) localisation were determined to be statistically significantly high in the benign group (p<0.05).

In the univariate analysis model, age, gender, hemoglobin, hematocrit, platelets, PCT, ferritin, LDH, sedimentation, CRP,

LAP located in the neck, the largest diameter of LAP in the neck, thorax LAP, axillary LAP, abdomen LAP, inguinal LAP, and the presence of splenomegaly, were observed to have a statistically significant effect on the differentiation of patients with benign and malignant LAP ($p<0.05$). The results of multivariate analysis showed that age, gender, PCT, sedimentation value, thorax LAP, and inguinal LAP were independently significant in the differentiation of patients with benign and malignant LAP ($p<0.05$) (Table 3).

Discussion

LAP develops due to an increase in inflammatory or neoplastic cells in the lymph node. Especially if it does not regress with antibiotic treatment or if there is suspicion of systemic disease, a biopsy must be taken. Although fine needle aspiration biopsy (FNAB) is helpful in benign-malignant differentiation, it is usually not sufficient for a definitive diagnosis [3]. When there is persistent LAP with a pre-diagnosis of lymphoma, excisional biopsy at the right time is the gold standard method. An approach that prevents unnecessary operations and does not delay the diagnosis of malignancy is the most appropriate [4]. The most important point at this stage is the availability of predictive markers that will guide the clinician.

Many studies in the literature have shown a relationship between age and malignant LAP [4, 5]. With increasing age, longer exposure to carcinogens, the formation of defects in tumor-suppressing genes, and a decrease in immunity increase the risk of malignancy. In the current study, the mean age of the group diagnosed with malignant LAP was seen to be 55.0±16.8 years, which was determined to be statistically significantly higher than the mean age of the group with benign LAP.

In a study by Chau et al., male gender was reported to be associated with malignancy [6], and there are data supporting this in other studies in the literature [7]. Consistent with these findings in the literature, male gender was determined to be statistically significantly correlated with malignancy in the current study.

For hemoglobin and hematocrit levels to be low, there needs to be infiltration that is chronic or has affected the bone marrow. These conditions are directly associated with malignancy. After discounting other causes of anemia, low hemoglobin seen together with LAP should alert the clinician in respect of malignancy. Supporting this theory, a relationship was determined between low hemoglobin/hematocrit and malignancy in the current study. In a study of pediatric patients, Sen et al. similarly determined a relationship between anemia and malignancy [8, 9].

LDH is an enzyme used in the cascade obtaining energy in the body. It is found in almost all tissues of the body and is determined to be high in the blood when there is tissue destruction for various reasons [10]. It is a parameter used in the prediction of malignant processes when especially high elevations are evaluated together with other supporting factors [5, 11, 12]. The results of the current study showed that the LDH level was found to be a statistically significant parameter in the prediction of malignant LAP.

There are various studies in literature related to the association with malignancies of thrombocytes and the thrombocyte parameters of PCT, mean platelet volume(MPV), and platelet distribution width(PDW), which can be easily evaluated in the full blood count. In a 2015 study, Özakşit et al. found no statistically significant difference in PCT between groups with benign and malignant adnexal masses [13], while Oncel et al. reported that PCT values were lower in lung cancer patients, consistent with the results of the current study [14].

LAP, especially generalized LAP accompanying thrombocytopenia, can reflect a malignant disease or a severe infectious process [15]. Similar to the current study, Al Kadah et al. found a relationship between thrombocytopenia and malignant lymph nodes [16]. PCT, which expresses the thrombocyte percentage, is expected to be low consistent with thrombocytopenia.

CRP is synthesized from hepatocytes in many rheumatological, oncological, hematological inflammatory, or infectious processes. It has been emphasized in many studies that there is an increase in CRP to accelerate the response to an inflammatory process in the environment, and this has been associated with a poor prognosis in malignant processes [17]. In the current study, a statistically significant relationship was determined between CRP and malignant lymph nodes.

A positive correlation between ferritin and the development of tumor cells and inflammation has been shown in many studies in the literature [18, 19]. The iron content and ferritin expression have been determined to be high in malignant cells. Supporting these data, it was seen that elevated ferritin can be used as a predictive parameter in the evaluation of LAP in the current study.

Folic acid deficiency is a cause of hypoproductive macrocytic anemia. In a study of 937 cancer patients, folic acid deficiency was determined at the rate of 7%, and in the hematological malignancy subgroup, this rate was found to be 9.5% [18]. Similar data were obtained in the current study and folic acid deficiency was found to be associated with mortality. In cancer patients, the reason for folic acid deficiency may be reduced oral intake, or folic acid deficiency as a cause of increased DNA mutation may cause malignancy.

Other than laboratory parameters in the evaluation of LAP, lymph node localization, and size are among the factors affecting prognosis In literature, a relationship has been found between malignancy and supraclavicular localization and involvement of more than two lymph node regions [6].In the current study, LAPs with neck, thorax, and abdomen localization, and the size of LAP localized in the neck were determined to be statistically significantly high in the malignant LAP group [20]. Celenk et al. found a relationship between left-side localized LAP and malignancy [7]. However, there are studies in the literature that have shown no difference between left and right-side localization in respect of the association with malignancy [4], or that have reported results showing a relationship between bilateral localization and malignancy [21]. In the current study, no statistically significant data were obtained on this point.

Splenomegaly develops in conditions such as diseases that result in hyperplasia (eg., infections, connective tissue disorders), infiltrative or deposition diseases, hemolytic anemia, or portal hypertension. In support of this, the current study data showed that if there is also splenomegaly when evaluating patients with

LAP, that there could be malignancy should be kept in mind [9].

Limitation

There are some limitations to our study. Since the study was conducted retrospectively, new-generation potential markers could not be evaluated. If the number of patients was larger, the statistics could have been stronger.

Conclusion

LAP can be frequently encountered as a reason for presentation at many departments of polyclinics such as Internal Medicine, Hematology, Ear, Nose, and Throat, and General Surgery. In a pathology encountered this often, biopsy and further testing of every patient may not be appropriate for reasons of both cost and workload. Therefore, predictive parameters will be of guidance to the clinician at the stage of decision-making. These parameters will avoid tiring the patient and the doctor with respect to unnecessary further tests, and the chance of early diagnosis will not be missed if it is a malignant process. This study aimed to investigate parameters that could show a predictive effect. In the results of the multivariate analysis, age, gender, PCT, sedimentation value, thorax LAP, and inguinal LAP were observed to be independently significant in the differentiation of patients with benign and malignant LAP ($p<0.05$). Rather than the use of these parameters singly, evaluation of them together would seem to be more beneficial with respect to specificity.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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